REMARKS

Claims 1-36, 38, 39, 43, 44, and 50-62 were preciously cancelled. Claim 46 was previously withdrawn. Applicants reserve the right to file divisional and continuation applications directed towards the cancelled and withdrawn subject matter. Claims 37, 40-42, 45, 47-49, 63 and 64 are currently under consideration.

Rejection Under 35 U.S.C. §103(a)

The Office Action states that claims 1, 4-6, 9 and 11 are rejected under 35 U.S.C. §103(a) as being obvious over Ogawa *et al.* (U.S. Patent No. 5,861,520; hereinafter "Ogawa") in view of Motoki *et al.* (Biol. Pharm. Bull., November 1995, Vol. 18, No 11, 1487-1491; hereinafter "Motoki") and Lin *et al.* (U.S. Patent No. 6,043,339; hereinafter "Lin"). However, these claims are not currently pending in this application. Applicants proceed with the understanding that this rejection pertains to pending claims 37, 40-42, 45, 47-49, 63 and 64. The Examiner states that Motoki teaches the administration of monosaccharide ceramides (including β-glucoceramide and β-galactoceramide) to a subject. The Examiner concedes that the subject contemplated in Motoki is not virally infected. *See* Office Action pages 3-4. The Examiner contends that Ogawa discloses the use of glycolipids to inhibit viral infections. The Examiner then states that while neither Ogawa nor Motoki teach *ex vivo* methods of treatment, Lin describes *ex vivo* delivery of glycolipids. *See* Office Action at pages 4-5. The Examiner then concludes that it would be obvious to combine the references because of the desire to improve drug delivery methods.

Applicants respectfully traverse the rejection. The recently revised Examiner guidelines for assessing obviousness set forth detailed requirements based on asserted rationales for obviousness. The Rationales To Support Rejections Under 35 U.S.C. §103 provide the following possible rationales:

> (A) Combining prior art elements according to known methods to yield predictable results;
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> (B) Simple substitution of one known element for another to obtain predictable results;
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> (C) Use of known technique to improve similar devices (methods or products) in the same way;

> (D) Applying a known technique to a known device (method or product) ready for improvement to yield predictable results;
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> (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
>
> (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; and
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

See MPEP 8th Edition, rev. 6, §2141. Applicant proceeds with the understanding that this rejection conforms to rationale G quoted above. The MPEP further sets forth the requirements for an obviousness rejection under this rationale:

> To reject a claim based on [rationale G], Office personnel must resolve the Graham factual inquiries. Then, Office personnel must articulate the following:
>
> (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
>
> (2) a finding that there was reasonable expectation of success; and
>
> (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.
>
> The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006). **If any of these findings cannot be made, then this rationale cannot be used to support**

> **a conclusion that the claim would have been obvious to one of ordinary skill in the art.** [emphasis added]

See MPEP 8th Edition, rev 6, §2143

As part of a *prima facie* case of obviousness, an examiner must establish some reason to combine the references. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 (2007); *Takeda Chemical Industries, Ltd. v. Alpharpharm Pty., Ltd.*, 492 F.3d 1350, 1356-1357 (Fed. Cir. 2007). The *KSR Int'l* Court acknowledged the importance of identifying a reason that would have prompted a person of ordinary skill in the art to combine the elements in the way the claimed invention does. *KSR Int'l*, 127 S.Ct. at 1731; *Takeda Chemical*, 492 F.3d at 1356-1357. Repeatedly throughout the *KSR Int'l* decision, the Court discussed the importance that the result obtained by a particular combination was predictable to one of ordinary skill in the art. *KSR Int'l*, 127 S.Ct. at 1731 and 1739-1742.

Applicants respectfully contend that he combination of the cited prior art references does not render the current claims obvious. As discussed previously, the Examiner states that Motoki teaches the administration of glycolipids, such as β-glucoceramide and β-galactoceramide. However, Motoki does not disclose the glycolipids as defined in the present invention. Motoki teaches the analysis of ten types of synthesized monoglycosylceramides (MonoCers) for the characterization of their immunostimulatory and anti-tumor properties. The compounds described in Motoki may be clearly differentiated from the compounds that are the subject of the present claims. In all cases, the present claims recite the use of a compound that must consist of a "mammalian intermediary metabolite". While the compounds described in Motoki may be chemically classified as glycolipids, these compounds would not fulfill the limitation of a "mammalian intermediary metabolite". The present application was published as U.S. Patent Application Publication No. 2004/0171528, as cited in the remainder of this paper. The '528 publication defines an intermediary metabolite as follows: "In the present invention, metabolites or intermediary metabolites are considered to be products of enzymatic processes in a mammalian system." *See* paragraph [0021]. Thus, a mammalian intermediary metabolite is a product that in its natural state is present in a mammalian cell. The existence of such compounds as a natural element in a mammalian cell is further enunciated later in paragraph [0021] with the

statement "Furthermore, such **elevated** levels of metabolites could also be obtained in the subject indirectly, either through enhancement of synthesis of the compound or inhibition of the degradation of the compound." (Emphasis added). Applicants assert that the term "elevated" has an implicit meaning of the existence of a basal level of the metabolite in a cell that is then raised by enhancement of synthesis or inhibition of degradation.

In contrast, the artificial nature of the compounds of Motoki is clearly described in the specification of that document. For instance, the abstract reads "Ten kinds of monoglycosylceramides (MonoCers), having the same ceramide portion and different sugar moieties, were **synthesized** and their immunostimulatory and antitumor activities were examined." (Emphasis added). This publication provides an extensive description of the synthesis of the MonoCers. *See* page 1487, right column, "MATERIALS AND METHODS, Synthesis and Physical Properties of MonoCers", extending to page 1489, right column.

Quite clearly, the compounds described by Motoki are not mammalian intermediary metabolites as they are synthesized compounds that are not found in nature (particularly in mammalian cells). The present claims require the administration of an effective amount of a mammalian intermediary metabolite. The compounds described in Motoki are not mammalian intermediary metabolites as defined by the present specification because they are not naturally occurring.

The deficiencies of Motoki are not cured by Ogawa. Like Motoki, Ogawa does not teach a mammalian intermediary metabolite as defined by the present invention. Ogawa teaches glycolipid analogs. For instance, the abstract reads "The present invention provides a compound which is a glycolipid **analog** having a **novel** structure represented by …: (Emphasis added). Further description of these non-native compounds may be found throughout the specification as follows: "An object of the present invention is to provide compounds which are glycolipid analogs with a novel structure…" Col. 2, lines 24-25; "The present invention relates to glycolipid analogs having a novel structure represented by the formula (1)…" Col. 4, lines 18-20. In fact, the compounds are repeatedly described as "glycolipid analogs" by the inventors. In addition, the specification contains abundant description of the synthesis of the analogs. See Examples 1 and 2, Test Examples 1-2, beginning at, Col. 12, line 13 and continuing to Col. 28,

line 67. Like Motoki, Ogawa does not teach mammalian intermediary metabolites as required by the present claims.

Lin also does not disclose the compounds of the present invention. Lin teaches a complex utilized for the delivery of biologically active molecules into the interior of a cell. This complex must be linked to an additional molecule, such as a linking peptide (*see* Abstract). The specification describes a complex linked to an importation competent signal peptide. See Col. 2, lines 38 - 46; Col. 3, lines 41-52. An "importation competent signal peptide" is defined at Col. 6, lines 32-60 as follows:

> An "importation competent signal peptide," as used herein, is a sequence of amino acids generally of a length of about 10 to about 50 or more amino acid residues, many (typically about 55-60%) residues of which are hydrophobic such that they have a hydrophobic, lipid-soluble portion. The hydrophobic portion is a common, major motif of the signal peptide, and it is often a central part of the signal peptide of protein secreted from cells. A signal peptide is a peptide capable of penetrating through the cell membrane to allow the export of cellular proteins. The signal peptides of this invention, as discovered herein, are also "importation competent," i.e., capable of penetrating through the cell membrane from outside the cell to the interior of the cell. The amino acid residues can be mutated and/or modified (i.e., to form mimetics) so long as the modifications do not affect the translocation-mediating function of the peptide. Thus the word "peptide" includes mimetics and the word "amino acid" includes modified amino acids, as used herein, unusual amino acids, and D-form amino acids. All importation competent signal peptides encompassed by this invention have the function of mediating translocation across a cell membrane from outside the cell to the interior of the cell. Such importation competent signal peptides could potentially be modified such that they lose the ability to export a protein but maintain the ability to import molecules into the cell. A putative signal peptide can easily be tested for this importation activity following the teachings provided herein, including testing for specificity for any selected cell type. (Internal citations omitted)

As described in detail above, the mammalian intermediary metabolite of the present invention is a natural element in a mammalian cell. The addition of a signal peptide in the form of 10 to 50 amino residues to a biologically active molecule clearly does not constitute a "natural element" existing in a mammalian cell. As with the previous two references cited by the Examiner, there

is no description in Lin of mammalian intermediary metabolites. Thus, the combination of the cited references does not result in the methods of the currently claimed invention, i.e., a process for treating a disease in a mammalian subject comprising the administration of cells treated with an effective amount of an intermediary metabolite or a reagent that increases the intracellular level of a mammalian intermediary metabolite in said cells. There is no motivation to combine the references and there would be no expectation of success that the combination of the references would result in Applicants currently claimed process. Withdrawal of the rejection is respectfully requested.

Conclusion

Applicants respectfully submit that all claims are in condition for allowance. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicants would appreciate the courtesy of a telephone call to their counsel at the number listed below to resolve such issues and place all claims in condition for allowance.

The Examiner is invited to contact the undersigned at 412-918-1100 to discuss any matter concerning this application.

The Office is hereby authorized to charge any additional fees or credit any overpayments under 37 C.F.R. § 1.16 or § 1.17 to the deposit account number 50-0525.

Respectfully submitted,

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